PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Attorney Docket No.: 2005.115US01

Eric John Gandras Confirmation No.: 7096

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For: PELVIC ARTERIAL CATHETER

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Paul C. Onderick, hereby declare and state as follows:

1. Included herewith is a true and correct copy of an article authored by Eric J. Gandras, M.D. entitled "The Gandras Catheter For Uterine Artery Embolization: The Procedure-Driven Development Of A Novel Medical Device." The article was published in *Minimally Invasive Therapy* in 2009.

I hereby declare that all statements made herein are of my own knowledge and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are

punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Executed this 28th day of July, 2009.

Paul C. Onderick
Registration No. 45,354

Customer No. 24113
Patterson, Thuente, Skaar & Christensen, P.A.
4800 IDS Center
80 South 8th Street
Minneapolis, Minnesota 55402-2100
Telephone: (612) 349-5766

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Original Article

The Gandras catheter for uterine artery embolization: The procedure-driven development of a novel medical device

Eric J. Gandras

Division of Vascular and Interventional Radiology, Department of Radiology, North Shore University Hospital – Manhasset, Department of Radiology, NYU School of Medicine, New York, NY, USA

Abstract

Uterine artery embolization (UAE) is a safe and effective therapy for women suffering from symptomatic fibroid tumors of the uterus. In order to complete the procedure, the interventionalist must be able to catheterize both uterine arteries from a single femoral puncture site. The uterine arteries are subsequently embolized, or occluded, to stasis by injecting small particles mixed with radio opaque contrast under fluoroscopic guidance. Historically, it has been necessary to use several different catheters of varying shapes, lengths and materials to accomplish the catheterization of both uterine arteries when performing UAE. Every catheter exchange increases the length and difficulty of the procedure. The risk and radiation dose of any interventional radiological procedure is directly proportional to its overall duration. Thus if a single catheter could achieve the objective of catheterizing the bilateral uterine arteries for UAE throughout the procedure, its use would decrease the length of the procedure and consequently decrease the overall risk to the patient, thus representing an improvement over the technology currently available. The purpose of this paper is to outline the anatomical and technical considerations that governed the development of an ideal catheter to perform UAE, the Gandras catheter.

Key words: *Fibroid, embolization, uterine, myoma, catheter*

Introduction

The story of uterine artery embolization (UAE) is well known and has been reported elsewhere (1). However, the serendipitous discovery first reported by Jacques Ravina in France in 1995 still makes for a compelling narrative. Ravina, a gynecologist, received patients for embolization prior to myomectomy or hysterectomy who were unable to give autologous blood donations preoperatively because they were too anemic. He noted that many patients cancelled their surgeries following embolization because their symptoms of heavy bleeding and pelvic pain had resolved. That seminal observation would lay the foundation for the establishment of UAE as a primary therapy for symptomatic fibroid disease. In 1998 the first procedure was performed in the United States at UCLA (2). Since those early pioneering days, UAE has proven to be a safe, effective and durable therapy for the treatment of symptomatic fibroid tumors of the uterus (3).

In 1999, when I first began performing UAE, the available catheters to complete the procedure included long reverse-curve catheters such as the MS-20 (Cordis, Miami, FL, USA) and standard push-forward catheters such as the Cobra catheter (Boston Scientific, Natick, MA, USA). Although some advocate using bilateral femoral arterialpunctures, most operators work via a right common femoral arterial approach. The anatomy of the uterine arteries is such that the contralateral, or left, uterine artery lends itself to catheterization most favorably with a push-forward design, such as that seen with a Cobra catheter. The ipsilateral, or right, uterine artery lends itself to catheterization most favorably with a long reverse-curve design, such as that seen with the MS-20.

A typical UAE procedure would require multiple catheter exchanges so that the contralateral artery would be catheterized and embolized using a Cobra catheter and the ipsilateral artery would be treated with an MS-20 catheter. Moreover, the uterine arteries

Correspondence: Eric J. Gandras, Associate Chief, Division of Vascular and Interventional Radiology, North Shore University Hospital-Manhasset, 300 Community Drive, Manhasset, NY11030
E-mail: Egandras@NSHS.edu

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are very prone to spasm, much like the renal or tibial arteries, upon catheterization. Even gentle use of the MS-20 catheter would frequently lead to severe spasm or, less frequently, dissection of the origin of the uterine artery, severely limiting the ability to complete the case. This problem could be circumvented by employing the use of a 3 French microcatheter placed coaxially through the larger catheters, deeper into the artery. Employing a microcatheter is also frequently used to avoid non-target embolization by deep-seating the tip within the uterine artery while minimizing spasm. However, the preferred embolic agent, polyvinyl alcohol particles (PVA), have a tendency to clump in smaller catheters and microcatheters. This clumping results in the need to further dilute the PVA, increasing the time of the procedure and contrast dose, as well as the possible need to exchange for another microcatheter. Microcatheters are quite expensive and can be cumbersome to use. Furthermore, the exchange may potentially result in losing a hard-fought position within an artery that, when placed into spasm, may not readily allow repeat catheterization.

The materials the Cobra and MS-20 are made out of are plastic polymers such as polyurethane and polyethylene. The tips are not very tapered and, the MS-20 in particular, is extremely rigid both throughout its shaft and at its tip. Although this reverse-curve catheter shape facilitated rapid ipsilateral catheterization, the stiff, untapered tip could easily lead to arterial spasm or dissection. Consequently, it became necessary to always use a microcatheter through the MS-20 unless the uterine artery was extremely large, either to avoid spasm or in an attempt to salvage the procedure despite spasm. These catheters were available in 5 French (MS-20 and Cobra) and 4 French (Cobra) diameters. The MS-20 is no longer commercially marketed.

Thus in 1999, completing a UAE procedure usually required using several different catheters of varying shapes, lengths and materials. Each catheter exchange increases the length and difficulty of the procedure. The risks of complications and radiation dose in any interventional radiological procedure are directly proportional to its overall duration in time. Therefore, if a single catheter could achieve the objective of catheterizing both uterine arteries throughout the procedure it would decrease the length of the procedure and subsequently the overall risk and radiation dose to the patient. Furthermore, it would make the procedure technically easier and faster for the operator and thus represent an improvement in the available technology.

Material and methods

In 1999 I found myself increasingly frustrated by the limits of the available technology. At the same time, I was inspired by the promise of UAE, especially after attending the annual SMIT meeting held in Boston in the fall of 1999. Although I had to drive through a hurricane from NewYork to get there, I was rewarded by being able to participate in an exchange of ideas with some of the pioneers in the emerging field of UAE, including Ravina himself. It was just a few months after this pivotal meeting that I conceived of the design for a solitary catheter that would potentially meet all of the needs of the operator performing UAE. Observations made regarding the anatomy and the behavior of the uterine arteries during catheterization led to the inspiration for the preferred embodiment of this ideal catheter to perform UAE. General considerations that would govern the development of this novel device included the following:

- The uterine arteries are prone to spasm.
- The uterine arteries are often tortuous.
- Spasm limits the ability to have good flow of embolic agent and contrast.
- Spasm tends to be worse when vessels are small and catheters are stiff.
- Uterine artery anatomy suggests a push-forward design for the contralateral artery and a reverse-curve design for the ipsilateral artery.
- The materials used should be soft and flexible at the point they engage the uterine arteries.
- In order to avoid clumping of embolic material the catheter should be as large as possible throughout most of its length. Only when it needs to enter or engage the uterine artery should it become smaller - therefore a tapered design is implied.
- The tip of the catheter needs to be seated deep enough within the uterine artery so as to avoid non-target embolization.

The goal was to combine the most favorable elements of the existing technologies available to create a solitary, novel and optimal catheter. Simply stated, the concept was to take the long reverse-curve shape of the MS-20, soften the material beyond the primary curve in order to make it more flexible, and add an elongated, ultra tapered tip that would function like a microcatheter at the end of the device. The flexible shaft of the catheter beyond the primary curve would minimize longitudinal force on the artery. The catheter would act like a shock absorber and bend when pulled ipsilaterally, as opposed to the stiffer existing catheters which would bend the artery, possibly leading to dissection, spasm or worse, arterial avulsion. An ultra tapered, hydrophilic tip would

allow for atraumatic catheterization. The hybrid, elongated distal tip would allow deep-seating within the artery, resulting in performance like a micro catheter without the steep costs, clumping, extra energy and time associated with its use. The low profile of the tapered tip should minimize spasm. The ideal catheter should remain large enough over a sufficient portion of its length to minimize clogging from the embolic agent. This would facilitate use with any embolic agent available, including gelfoam pledgets and slurry, with minimal risk of catheter occlusion.

The overall length of the catheter, the length of the catheter beyond the primary curve and the length of the distal tip were all determined based upon observations and measurements derived from pelvic arteriograms from UAE procedures, as well as other types of arterial interventions. The specifications of the device represent compromises based upon the variable anatomy encountered in clinical practice - some aortic bifurcations are steep while others are shallow. Some uterine arteries are downward in direction and some arise at an acute, or even right, angle. Some uterine arteries are large, tortuous and long and others are small, straight and short. The idea was to have a device whose dimensions could serve the majority of the anatomic variants encountered.

The original concept was to literally have a microcatheter tip added on to a 5 French tapered to 4 French catheter. Initial ideas to achieve this included having the tip telescope out the end of the catheter or, alternatively, construct the tip as a modular component that could be affixed to the catheter with the option of selecting varying lengths of micro catheter tip, depending upon the anatomy of a given patient. This would provide a truly customized medical device for the individual patient, leading to a more efficient, safer procedure. The existing technology, however, would not allow for a taper to a 3 French level, regardless of the above-mentioned designs.

The materials for the initial 5 French component could be polyurethane or any standard polymer used for existing catheters. The softer component arising beyond the primary curve could be composed of a softer plastic such as Pebax in order to allow conformational changes in the catheter, particularly when pulling it into the ipsilateral artery, in order to minimize trauma to the artery. Tungsten or barium could be impregnated into the catheter to improve radioopacity at fluoroscopy. Although a braided design would improve torqueability, there would be disadvantages associated with braiding the catheter such as rigidity and kinking that would eventually lead to abandoning this element.

Results

A medical device company initially manufactured the catheter customized to my specifications in 2000. Between 10 and 15 prototypes were trialed over a one to two year period before a satisfactory device was achieved. An improved version has more recently been developed, manufactured and launched onto the market by Vascular Solutions (Minneapolis, MN, USA), one in which the original concept of the elongated, ultra tapered tip has been actualized. The original prototype was only available with a tip length of 1.5 cm. The Vascular Solutions version is available in 2, 4 and 6 cm tip lengths (Figure 1).

The only catheter previously marketed specifically for UAE is the Roberts Uterine Catheter, or RUC (Cook, Bloomington, IN, USA). Although the RUC, like the Gandras, has its roots in the MS-20 and earlier long reverse-curve catheters, there are several important differences between the two devices. First, the Gandras is available in a variety of tip lengths whereas the RUC has only one. The tip lengths of the Gandras catheter are 2, 4 and 6 cm, all longer than that of the RUC. The length of the distal tapered segment is longer on the Gandras. The length of the soft, flexible material (Pebax) beyond the primary curve is 10 cm to the secondary curve on the Gandras, which is considerably longer than the corresponding segment of the RUC. The overall lengths of all of the versions of the Gandras are shorter than the RUC. The distance from the primary to the secondary curve on the Gandras catheter is 15 cm, whereas the corresponding distance on the RUC is 20 cm. Finally,

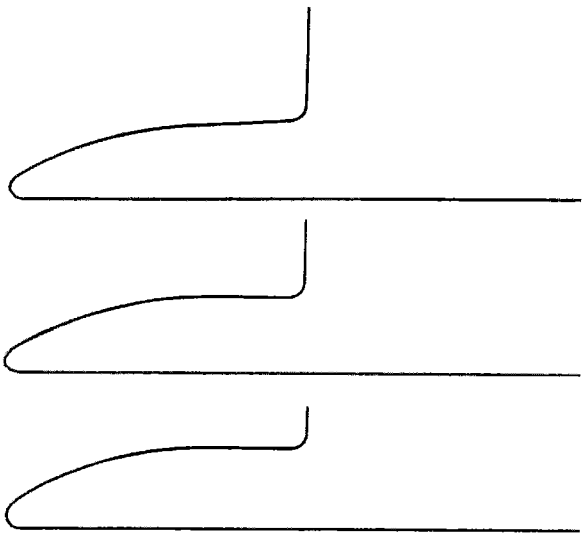

Figure 1. The Gandras catheter in 2, 4, and 6 cm tip lengths.

the Gandras is not a braided catheter. The performance advantages of the above-mentioned Gandras design elements have been and will further be discussed throughout this article.

In clinical practice the Gandras catheter has exceeded all expectations. That is, it has allowed others and myself to complete UAE procedures efficiently, safely, relatively easily and without having to resort to microcatheter use in the majority of cases encountered. Microcatheter use has been nearly completely eliminated because the distinctive features of the Gandras allow for deep seating while minimizing spasm. The initial prototype has been used from 2000 up until March 2008, at which time the Vascular Solutions version received FDA approval for use. Since March 2008 until the present, I have been using the Vascular Solutions catheters with improved performance compared to the initial device, with a technical success of 100% in catheterizing the bilateral uterine arteries from a single femoral puncture site and completing the UAE procedure. The original prototype was placed with difficulty over the aortic bifurcation when the bifurcation was very steep. Because it was a braided catheter it would not allow itself to be advanced deep enough into the contralateral artery. In addition, when the bifurcation was shallow, occasionally the catheter would kink at the primary curve. The newer version is not braided and as a result, the above-mentioned problems have not been encountered.

The author's data from catheter use since 2006 are listed in Table I. The overall technical success of catheterizing both uterine arteries from a single femoral puncture site using only the Gandras catheter is 84%. When this number is stratified comparing the original prototype to the newer version, the results are telling. The technical success of the original prototype is 77%. The technical success with the newer Vascular Solutions catheter is 100%. In all nine technical failures, the original braided prototype was used. Reasons for failure included, as mentioned above, the presence of a steep aortic bifurcation, small uterine arteries and sharp angulation of the origin of the uterine artery. In five of these nine patients, ipsilateral catheterization with the Gandras catheter could be performed. A microcatheter was required in only 4% of all cases. These patients had very small uterine arteries, with one patient requiring a repeat UAE which revealed small collateral vessels arising from the anterior divisions of the internal iliac arteries. At the time of this writing the estimated cost of a microcatheter in the U.S. is approximately $300.00. Therefore the overall cost savings resulting from avoiding microcatheter use in 96% of cases is approximately $15,600.00.

Discussion

In the field of Interventional Radiology, technology often drives the development of new procedures. Alternatively, the effectiveness of a procedure can drive the development of technology. UAE has an extremely favorable risk/benefit profile, and it was apparent early on that the promise of this procedure would be fulfilled. However, there has been a void in the existing technology with respect to the ideal catheter needed to perform the procedure. The technique for performing UAE has remained essentially the same since the late 1990s. As a result, the challenges confronting me and other operators in 1999 in completing UAE are the same ones confronting us today. That is, one needs to catheterize both uterine arteries from a single puncture site, place a catheter deep enough into the uterine artery so as to avoid non-target embolization, avoid arterial spasm when engaging the uterine arteries and deliver particulate embolic agents without having them clump in the catheter. In order to fulfill these requirements, operators often need to use a variety of catheters and microcatheters to complete the procedure. In addition, because of the anatomic variation between the left and right uterine arteries, the two sides favor different types of catheter shapes. The devices previously available have allowed the operator to engage the origin of the uterine artery but frequently have not allowed deep-seating because of spasm or dissection, thus necessitating microcatheter use, particularly in medium-sized or smaller arteries. Additionally, the inherent tortuosity in arteries supplying a myomatous uterus requires flexibility if the catheter tip is going to be placed deep. The Gandras catheter was designed with all of the above considerations and challenges in mind. It has been developed and further refined to satisfy the need for an improved solitary device in order to perform UAE more safely and more efficiently.

The technical success of the Gandras catheter compares favorably with the few published studies regarding devices used for UAE. In 2005, Ho reported a technical success of 79% using the Rosch inferior mesenteric (RIM) catheter to catheterize the bilateral uterine arteries via a right common femoral approach in 72 patients (4). In 2007, Kroencke reported a technical success of 89% in 364 patients in which the RIM catheter was used for bilateral pelvic catheterization via a right common femoral approach (5). However, in this larger series a microcatheter was used in 81% (295/364) of the cases. A letter to the editor in JVIR in 2007 described using a 5 French Tight Curve catheter along with a microcatheter for UAE (6). The authors stated, "[t]

Table I. The Gandras catheter in clinical practice since 2006.

	Technical success in catheterizing bilateral uterine arteries from single femoral puncture site	**Cases in which microcatheter use was required**	**Cost savings from avoidance of microcatheter use with unit cost approx. $300.00/unit**
Original prototype catheter (Jan 2006-April 2008)	30/39 (77%)	2/39 (5%)	$ 11,100.00
Vascular Solutions catheter (April 2008-September 2008)	16/16 (100%)	0/16 (0 %)	$ 4,800.00
Overall combined performance	46/55 (84%)	2/55 (4%)	$ 15,900.00

here is no single ideal catheter or approach for the UAE procedure." Fortunately there remains room for progress regarding catheter performance in UAE and the Gandras catheter has arrived to fill this niche. Initial clinical success is encouraging and hopefully the working interventionalist will find this catheter a useful tool to help treat their patients safely and effectively.

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